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RESPONSE OF EPIDERMOID AND NON-EPIDERMOID CANCERS OF THE HEAD AND NECK TO FAST NEUTRON IRRADIATION: THE FERMILAB EXPERIENCE*

Parvathy D. Kurup, M.D., JoAnne Mansell, R.N., P.A.,
Randall K. Ten Haken, Ph.D., Frank R. Hendrickson, M.D.,
Lionel Cohen, M.D., Miguel Awschalom, Ph.D., and
Ivan Rosenberg, Ph.D.

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ABSTRACT

One hundred and six patients with locally advanced cancers of the head and neck were treated with neutrons at the Fermilab Neutron Therapy Facility. Of these, 44 patients were previously untreated, 33 were recurrent following attempted surgery and 29 patients had previously received a full course of radiation therapy with conventional radiation. Results were analyzed to study the influence of stage, previous management, site of origin and tumor histology on local control of the disease. The most significant factor determining the outcome in this series of patients is the histological type. For epidermoid carcinoma, long term local control was achieved in 17/35 patients (49%) in the previously unirradiated group. With non-epidermoid tumors (adenocarcinoma, cylindroma, muco-epidermoid carcinoma), the local control rate was 28/39 (72%). Disease-free survival analysis also shows a survival advantage in non-epidermoid lesions treated with neutrons. It is concluded that neutron beam therapy is probably the treatment of choice for non-resectable or recurrent non-epidermoid cancers of the head and neck.

INTRODUCTION

Patients with carcinoma of the head and neck region often present with advanced lesions which are difficult to control by conventional irradiation or surgery. A combination of radical surgery and radiation frequently results in disfigurement and functional impairment, necessitating elaborate reconstructive procedures. The difficulty in achieving good local control with conventional irradiation is thought to arise, in part, from a significant hypoxic cell population in large tumor masses. Hence, alternatives such as high-LET radiation, radiosensitizers,[35] hyperbaric oxygen[16] and hyperthermia[27] have been tried in recent years. Catterall and Bewley first reported encouraging results utilizing fast neutrons in a controlled clinical trial on locally advanced head and neck cancers.[7,8] Other centers have since reported varying results.[5,12,13,15,17,20,22-25,34] This report analyzes the results of fast neutron irradiation at Fermilab (near Chicago, Illinois) for locally advanced and recurrent carcinoma of the head and neck.

METHODS AND MATERIALS

Between September 1976 and December 1980, 106 patients with locally advanced or recurrent head and neck cancer were treated with fast neutron irradiation at the Fermilab Neutron Therapy Facility. Of these, 44 patients were previously untreated. Of the 62 patients with recurrent disease, 33 had surgical resection done in the past. Twenty-nine patients had been treated previously with full course low-LET irradiation either alone or with surgery. Informed consent was received from all patients after the nature of the treatment program was fully explained to them.

Treatment Policy and Technique

At the Fermilab Neutron Therapy Facility fast neutrons are produced by bombarding a 22 mm thick beryllium target with 66 MeV protons from a linear accelerator.[2,4,10] The relative biological effectiveness (RBE) of this beam is approximately 3.0.[26,29] Its skin sparing and depth dose characteristics are similar to those of 8 MeV X-rays.[3,30,33] Patients are treated in a sitting position in an adjustable chair.

Immobilization of the head is achieved with individually made "Light Cast" molds.* The neutron beam is fixed horizontally. All the relative movements provided by conventional isocentric therapy can be achieved with the chair, since it moves in three dimensions and rotates about a vertical axis. The point of intersection of the vertical axis of rotation and the central axis of beam defines the isocenter, which is at 190 cm from the target. Four intersecting laser beams help in proper alignment of the patient.

X-rays for planning are taken while the patient is sitting in the same chair. Treatment plans are individualized for each patient, depending upon the tumor site of origin and involvement of lymph nodes in the neck. The target volume consists of gross tumor with at least a 1 cm margin. The neutron doses reported are "target absorbed doses"[18] including the gamma component. Doses were usually prescribed in terms of minimum target volume doses which varied from 20 Gy to 24 Gy; nominal target absorbed doses were generally 10% higher. The regional lymph node areas at risk were treated to a dose of 14 - 15 Gy, limiting the spinal cord dose to less than 12.5 Gy.

*Light Cast, Merck, Sharp & Dohme, Orthopedics Co., Inc., Costa Mesa, CA.

A typical treatment plan for central disease with unilateral adenopathy is shown in Fig. 1.[4] The treatments were given two or three times every week for six or seven weeks. Multiple fields, including posterior oblique fields, wedges and bolus were used as needed. Patients with major salivary gland tumors were treated over a period of four weeks using mostly a "wedged pair" technique.[4,20]

All patients were seen in follow-up at 2-3 month intervals. Any necessary diagnostic work-up was done at referring institutions.

Patient Population

Patients with head and neck cancer treated with fast neutrons alone with curative intent up to December 1980 are included in this analysis. For the previously untreated patients, lesions are staged using the AJCC system.[1] The distribution by initial T + N staging is shown in Table 1. Most of them had stage IV lesions. The initial treatment for the patients with recurrent disease consisted of partial resection (12), radical surgery (16), or full course low-LET irradiation (29). Five patients were treated for residual disease post-operatively.

Table 2 is a classification of all patients according to the tumor site and histology. Most tumors had originated in the oral cavity and oropharyngeal regions. Tumors arising from major and minor salivary glands were also included. The non-epidermoid carcinomas were adenocarcinomas or mucoepidermoid carcinomas.

RESULTS

Local Control

Complete absence of detectable tumor in the primary site and regional lymphatic drainage areas is considered as local control. If clinical evaluation was equivocal, biopsies were done to determine the local status.

For the previously untreated group of patients, local control was analyzed according to the initial stage of lesion, as shown in Table 3. In the 41 previously untreated patients, 23 were controlled (56%). The importance of initial stage as a prognostic factor is shown; good local control was obtained with earlier stage lesions.

Of the 62 patients who had recurrent disease, the overall local control rate is 31/62 (50%) (Table 4). However, further breakdown according to previous treatment reveals that in the subgroups of patients who were treated after surgery the local control rate is 23/33 (70%) compared to only 8/29 (28%) in the previously irradiated group. The extent of surgery also appears to influence the results, shown by the small subgroups in Table 4.

The influence of site of origin and histology of tumor in the local control of disease was also analyzed. As shown in Table 5, non-epidermoid lesions have shown a consistently better response. Further analysis of this was done according to the previous treatment and extent of residual disease, since many had recurrent lesions (Table 6). In subgrouping, according to the extent of disease, we have used the term small recurrent/residual disease (Table 7) for gross residual or recurrent disease measuring up to 5 cm in size. In some cases residual disease was spread out in more than one area. Massive recurrent disease was defined as disease measuring over 5 cm in size. Computerized tomographic scans were useful in making these measurements. Nineteen out of 24 patients (79%) with recurrent non-epidermoid lesions after surgery achieved local control; 5/9 with massive recurrence after surgery have local control of disease (Table 7). Fig. 2 graphically represents the actuarial analysis of local control.[6] The difference in local control of disease between epidermoid and non-epidermoid lesions is statistically significant (Log-Rank Method)[28] with a P value of less than

.001. With epidermoid lesions most of the local failures have occurred in the first 12 months. Recurrences in the non-epidermoid group have occurred up to 36 months after treatment.

Survival

At the time of analysis 41/106 patients are alive, 34 of them with local control of disease. The median follow up for all living patients is 2 years. Actuarial disease-free survival[6] for the two groups according to histology is shown in Fig. 3. The survival is not adjusted for intercurrent disease (all deaths are assumed to be cancer related). The two curves are significantly different (Log-Rank method, P value of less than .001).[28] Patients with non-epidermoid lesions have longer disease-free survival. An uncontrolled primary with or without regional and distant disease was the major cause of death (Table 8). Distant disease alone was the cause of death in only a few patients. Of the 11 patients with epidermoid tumors who died of intercurrent disease, 9 died within 12 months. Two patients with non-epidermoid tumors died at 3 and 4 years after treatment of apparently unrelated causes.

Morbidity

Details of major treatment morbidity are summarized in Table 9. Patients who died without significant complications within 5 months of treatment are considered ineligible for late morbidity analysis. The 29 patients who received prior treatment with low-LET radiation are also not included. The RTOG/EORTC late radiation morbidity scoring scheme is used. Soft tissue necrosis or ulceration at the primary site is not scored as a treatment complication when it is associated with persistent tumor. Persistent ulceration, bone necrosis, symptomatic fibrosis and severe xerostomia that needed medical or surgical intervention are scored as major complications. Of the 71 evaluable patients 13 developed significant complications (18%). It will be noted that in all but one of these patients the target absorbed dose exceeded 25 Gy. Bone necrosis in 3/5 patients was precipitated by tooth extraction or mandibular drilling and all were sucessfully treated by conservative management or surgical excision.

In two patients who developed loss of vision, the original extent of disease had necessitated inclusion of the whole ipsilateral eye in the target volume. Soft tissue necrosis in the larynx and trachea caused fatal complications in 2 patients: one developed recurrent tumor of the trachea after surgical resection; the other developed necrosis of laryngeal structures following repeated biopsies.

DISCUSSION

More than half of our patients were referred for treatment of recurrent disease after surgery or radical radiation therapy. Most of the previously untreated patients had Stage IV disease. Many published reports deal with neutron treatment of late stage patients,[5,7,8,12,13,15,17,20,22-25,34] and reports from the M.D. Anderson Hospital[24,25] have also included patients with recurrent tumors. Our results compare favorably with those from other centers (Table 10) with the exception of the striking improvement in local control with neutrons shown in the randomized trial from Hammersmith.[7,8] The observed differences may be related to treatment policies. At Hammersmith the target volume is designed to encompass the gross tumor; uninvolved areas are not included prophylactically. Hence, dosage gradients are more uniform. This probably has resulted in a higher minimum tumor dose with better tolerance of normal tissues. Whether this policy would yield increased failures in regional and distant sites has not been determined. Certainly no survival advantage has been demonstrated. However, survival depends on many other factors including distant metastases as well as non-tumor related factors like age and intercurrent disease.

Analysis reveals a somewhat increased occurrence of major morbidity for the neutron treated group in comparison to other groups in our experience (unpublished data). This has also been the experience in other centers.[5,12,13,22-25] The effect is dose-related and morbidity is low when doses do not exceed 25 Gy.

Cohen[11] has studied the dose response relationship for neutron beam therapy of epidermoid cancer at Fermilab and suggests that no further improvement could be obtained by adjusting the dosage alone. It may be that smaller target volumes and higher minimum tumor doses will improve the prospects of "uncomplicated" local control, since dose-effect curves with neutrons are steep for both tumor control and complications. New studies with fast neutrons for head and neck cancer are designed to evaluate different doses with shorter overall treatment time (4 - 4-1/2 weeks compared to 6 - 7 weeks), similar to the Hammersmith regimen. In this series, a major effort will be made to achieve as homogenous a dose in the target volume as possible.

The observed difference in local control between epidermoid carcinoma and other histological types prompts us to evaluate other factors like previous treatment, site of origin and stage in the latter group. Since the numbers are small and the difference is mainly in the group with recurrent disease after previous surgery, it is difficult to determine whether the tumor volume is the major contributing factor. The mixed-beam study from M.D. Anderson[24,25] included non-epidermoid carcinomas; it was believed that because of small numbers the overall results would not have been affected. European studies[12,13,34] were confined to epidermoid carcinomas, with the exception of the Hammersmith[7,8] series which might have included other histologies. In this series, most failures in epidermoid lesions occurred the first year, while the non-epidermoid group has shown recurrences up to three years. Since adenocarcinomas are generally considered less radioresponsive to conventional radiation, any improvement in this group with fast neutrons may afford a real advantage. Most non-epidermoid carcinomas in our series (Table 2) were salivary type tumors arising from major salivary glands or presumed to have arisen from minor salivary glands. The efficacy of fast neutron therapy for salivary gland tumors is well established.[5,8,17,20]

We have not done a randomized study comparing conventional radiation therapy with fast neutrons for non-epidermoid tumors. However, in reviewing the literature, results with definitive conventional radiation therapy are not very encouraging in the treatment of non-epidermoid tumors of the head and neck. Local control rates for non-resectable, recurrent and gross residual disease range from 10-40% in most published series.[9,14,19,31,32] Kagan et al[19] has reported that in recurrent malignant salivary gland tumors conventional treatment is usually ineffective in 3/4 patients. The M. D. Anderson experience in treating malignant tumors of major salivary glands with conventional radiation was reported by King and Fletcher.[21] Control of disease above the clavicle was achieved in 70/93 patients (75%). Of these, 19 patients were treated prophylactically and 27 for post-operative residual disease after surgery. Seventy Gy or more was used for unresectable and gross residual disease in this series. With doses in that range Chung et al.[9] have reported control of disease in only 4/10 patients. A comparison of results in previously untreated epidermoid carcinomas of head and neck utilizing neutrons, including mixed beam procedures, was done at our Facility (unpublished data). We could not establish any superiority for fast neutrons or a combination of photons and neutrons as compared to photons alone. There was only a minimal improvement in local control in the neutron group, but this group also had the highest rate of treatment-related morbidity. The results of a randomized RTOG study indicates that mixed beam irradiation is superior to conventional photon radiation for the treatment of cervical adenopathy from epidermoid carcinomas of the head and neck region.[15]

It is concluded that fast neutron therapy for locally advanced head and neck cancer is at least as good as conventional radiation and may be slightly superior in recurrent (after surgery) lesions. In previously irradiated patients, tolerance and control are poor. Neutron beam therapy may turn out to be the treatment of choice for non-resectable and recurrent non-epidermoid cancer of the head and neck.

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Table 1

Head and Neck Carcinoma - Neutrons Only

Distribution According to Initial Staging

T \ N	N0	N1	N2	N3	Total
Tx	-	-	1	1	2
T2	7	-	2	1	10
T3	6	4	3	4	17
T4	7	1	1	6	15
Total	20	5	7	12	44

Stage II - 7, Stage III - 10, Stage IV - 27.

Table 2

Head and Neck Carcinoma - Neutrons Only

Distribution According to Site and Histology

SITE	Epidermoid	Other*	Total
Oral Cavity	18	7	25
Oropharynx	17	5	22
Larynx	8	0	8
Hypopharynx	8	0	8
Nasopharynx	1	1	2
Paranasal sinuses	3	6	9
Prim. unknown or other sites	4	3	7
Major salivary glands	0	25	25
TOTAL	59	47	106

*Other - adenocarcinoma, mucoepidermoid carcinoma, malignant mixed carcinoma.

Table 3

Head and Neck Carcinoma - Neutrons Only

LOCAL CONTROL VERSUS STAGE

(a) T-N Classification

N \ T	Tx	T2	T3	T4	Total
N0	-	5/6*	3/6	1/7	9/19
N1	-	-	4/4	0/1	4/5
N2	- *	2/2	3/3	- *	5/5
N3	0/1	1/1	3/4	1/6	5/12
Total	0/1	8/9	13/17	2/14	23/41 (56%)

* - 1 unknown.

(b) Stage

Stage II	5/6
Stage III	7/10
Stage IV	11/25

Table 4

Head and Neck Carcinoma - Neutrons Only

LOCAL CONTROL VERSUS PREVIOUS TREATMENT

Previous Rx	Local Control	
Surgery	23/33	(70%)
Partial	10/12	
Radical	9/16	
Post-Op	4/5	
Radiation Therapy and Surg.	8/29	(28%)
Total	31/62	(50%)

Table 5

Head and Neck Carcinoma - Neutrons Only

Local Control Versus Site and Histology

Site	Epidermoid	Non-Epidermoid	Total
Oral Cavity	3/18	6/7	9/25
Oropharynx	6/16	3/5	9/21
Larynx	5/8	-	5/8
Hypopharynx	5/7	-	5/8
Nasopharynx	0/1	0/1	0/2
Paranasal	1/3	3/6	4/9
Prim. Unknown	0/3	3/3	3/6
Maj. Salivary Glands	-	18/25	18/25
TOTAL	20/56 (36%)	33/47 (70%)	53/103 (52%)

Table 6

Head and Neck Carcinoma - Neutrons Only

Local Control by Histology & Previous Treatment

Histol. / Prev. Treatment	Epidermoid Carcinoma	Non-Epidermoid Carcinoma	
		Major Salivary Gland	Other
None	13/26	4/6	5/9
Surgery	4/9	10/14	9/10
Radical Radiation Therapy ± Surg.	3/21	4/5	1/3
Total	20/56 (36%)	18/25 (72%)	15/22 (68%)

Table 7

Head and Neck Carcinoma - Neutrons Only

LOCAL CONTROL IN NON-EPIDERMOID GROUP
WITH PREVIOUS SURGERY

Disease	Local Control
Post-Operative (Microscopic Residual)	3/3
Small Recurrent/Residual	11/12
Massive Recurrent	5/9
TOTAL	19/24 (79%)

Table 8

Head and Neck Carcinoma - Neutrons Only

Cause of Death

Died with disease, primary ± Reg, ± distant metastases	43
Died with distant metastases, (local & regional NED)	9
Died of unrelated causes	11
Died with radiation therapy complications	2
Total	65
Alive	41/106

Table 9

Head and Neck Cancer

Neutrons Only

<u>Major Morbidity</u>

Morbidity	Number of Patients	Max. Dose to Critical Structures (Gy neutrons)	Comments
Bone Necrosis	5	15.0, 25.7, 25.3 26.7, 27.5	Precipitated by tooth extraction 3/5
Soft tissue & cartilage necrosis	3	26.7, 26.8, 26.3	Fatal in 2 patients
Severe symptomatic fibrosis	2	26.9, 26.5	Surgical excisions in the past
Loss of vision	2	26.9, 26.9	Eye treated for lesion of max antrum
Cerebellar necrosis Peripheral neuropathy	1	28.0	Craniotomy done. Alive with metastases
TOTAL	13	25.8 (mean)	

Table 10

Head and Neck Cancer - Neutrons Only

Local Control Results from Different Centers

Hammersmith[7,8]	Houston[24,25]	EORTC*	Fermilab No Prev. RT.	Fermilab Prev. RT.
53/70 (76%)	23/49 (47%)	48/100 (48%)	46/74 (62%)	8/29 (28%)

*EORTC - European Organization of Radiation Therapy Centers, J. Battermann, Secretary, written communication, Feb., 1982.

List of Figures

Figure 1

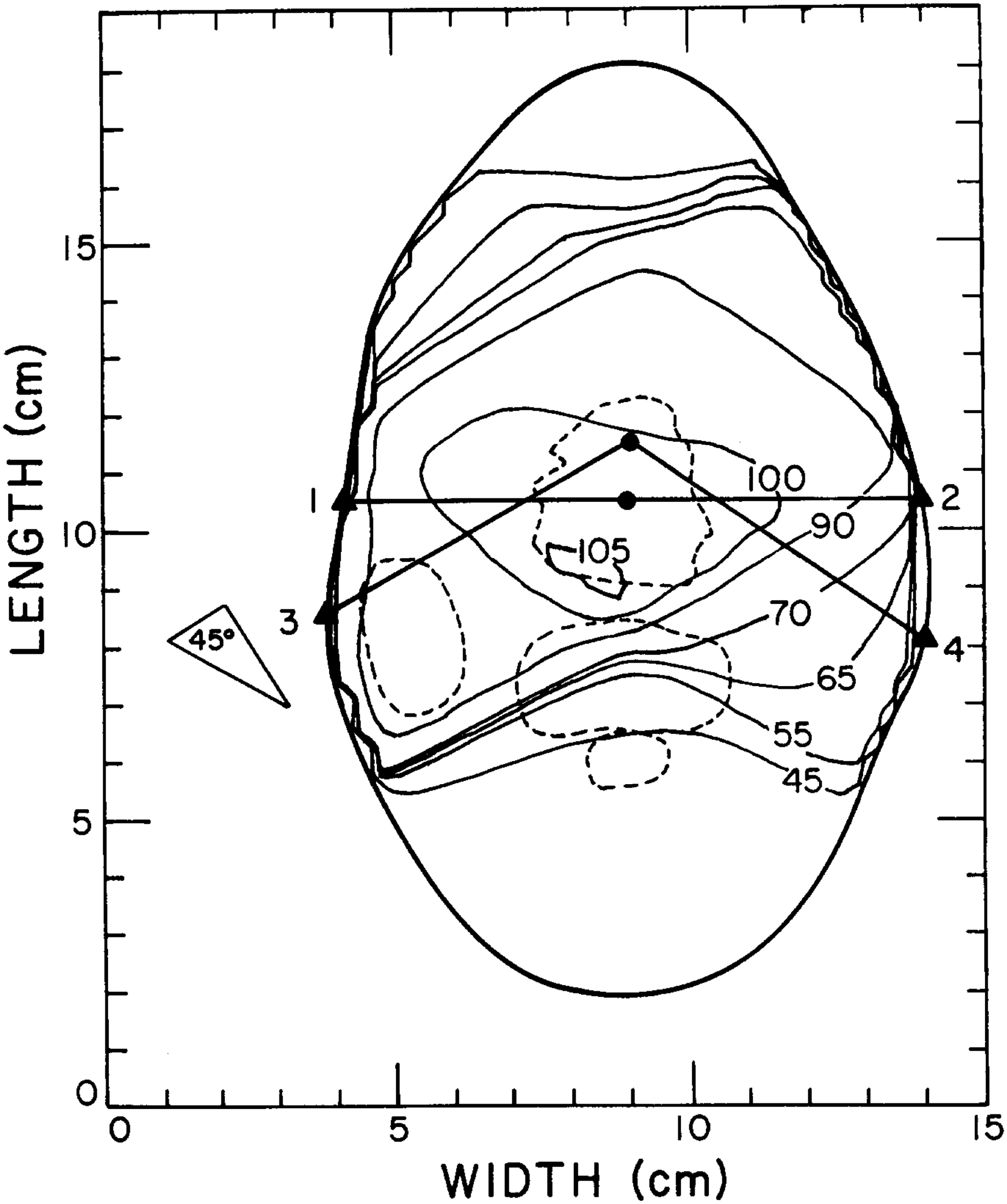

Figure 2

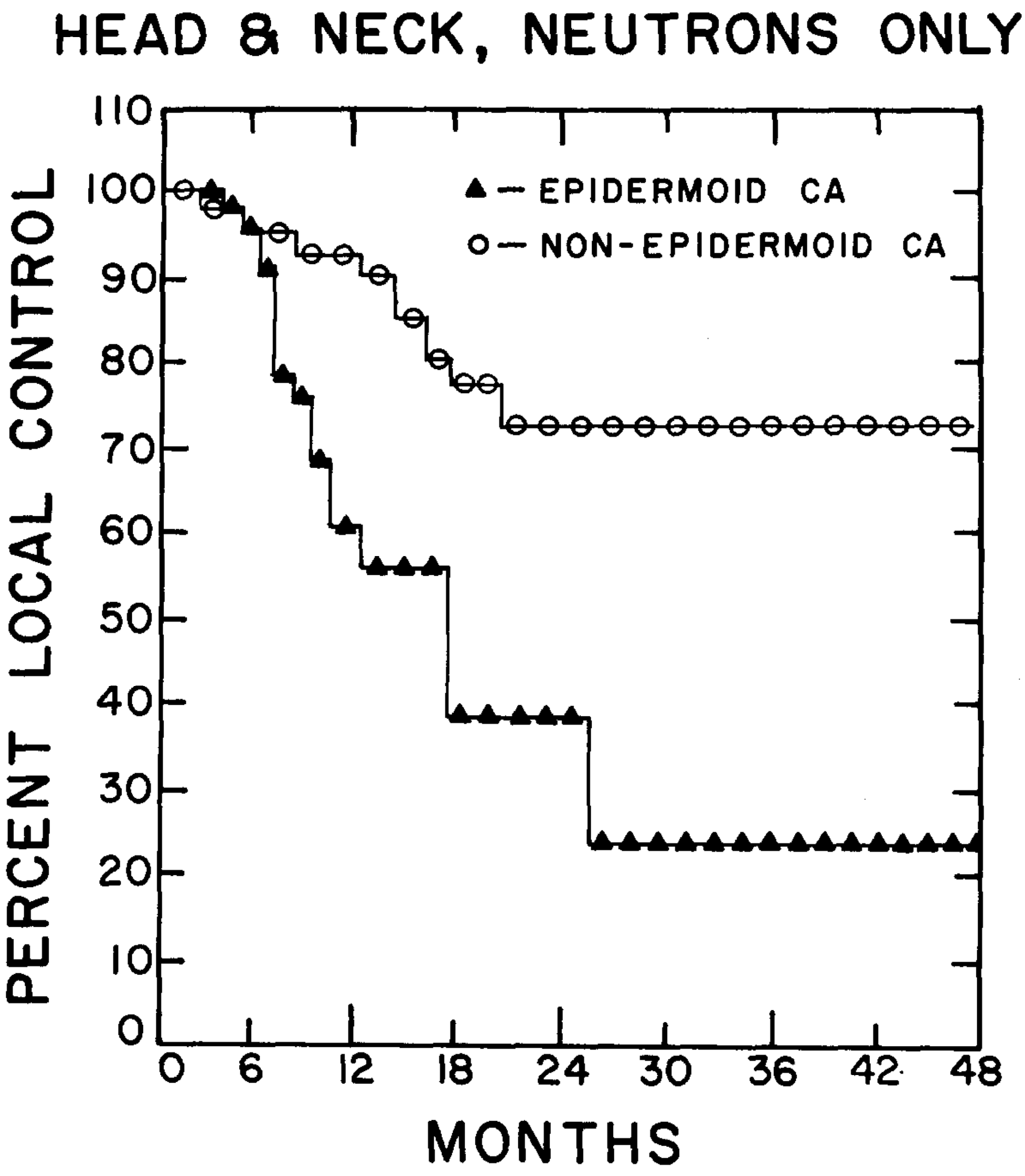
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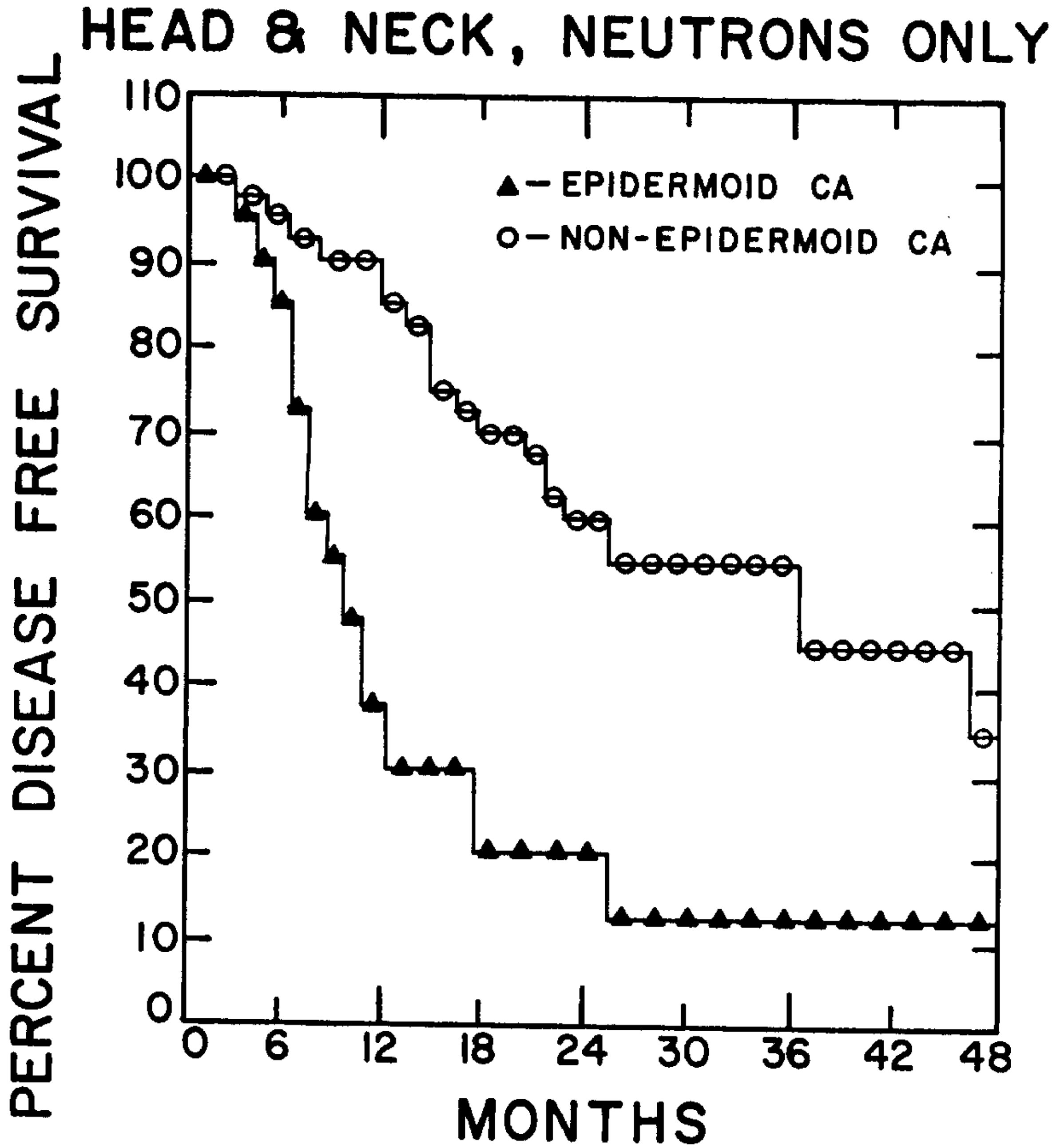
Figure 3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